Z represents an NH_2 group, a monoalkylamino group having up to 7 carbon atoms, a dialkylamino group having up to 7 carbons, a piperidinyl or morpholinyl radical which is attached via the nitrogen, hydroxyl, alkoxy having up to 7 carbon atoms, acyloxy having up to 7 carbon atoms or aroyloxy having 6 to 10 carbon atoms,

B2 cont C2 cont

and the substituents listed under X, Y, R^1, R^2, and R^3 and/or A are modified or introduced by acylation and derivatization of free amino groups, chlorination, catalytic hydrogenation, reduction, oxidation, removal of protective groups and/or nucleophilic substitution.

Remarks / Arguments

As a result of this amendment, claims 1-8, 10-11, and 13-21 are pending in the application. Claim 6 has been amended. No new matter has been added.

Regarding the specification

In response to the examiner's comment that the specification does not include a description of the drawing, text describing Figures 1 and 2 has been inserted into the specification on page 1.

The rejection under §112

The examiner rejected claims 1-8, 10-11, and 13-21 under §112, second paragraph, as being indefinite, on the grounds that a) the language "up to" used to define the possible number of atoms in a group is unclear as to the range intended, b) the term "medicaments" could mean either a pharmaceutical composition or a product compound, and c) in claim 6 the group "D" of structure (II) was incorrectly defined.

Regarding the language "up to", applicants maintain that this terminology is sufficiently clear to be understood by those skilled in the art, and accordingly, request that the rejection be withdrawn.

Whenever the language "up to" is employed in this application, the type of group is named. The minimum number of the atoms under consideration is provided by the chemical nomenclature identifying the group. For example, "alkyl having up to 6 carbon atoms" would mean an alkyl group having a minimum of 1 carbon atom because the smallest possible alkyl group is methyl, which has one carbon.

For a given named group, the upper limit for the number of atoms under consideration is provided by the number following the language "up to". The language "up to" is a direct translation from the original German "bis zu". According to a German dictionary (copies of relevant pages being included with this response), when used in the context of such things as age, measures, quantities or amounts, or temperature details, the language "bis zu" means "up to" and indicates a maximum. An example given by the dictionary is "Gefängnis bis zu 8 Jahren", which translates to "a maximum of 8 years imprisonment". It is thus clear that the language "up to" in the present context is meant to define the maximum permitted number of the atoms under consideration.

To summarize, in accordance with the above two paragraphs, the exemplary language "alkyl having up to 6 carbon atoms" would mean alkyl having from a minimum of 1 to a maximum of 6 carbons. The same logic should apply to interpretation of the phrase "up to" in the several instances in which it is used in the present specification and claims.

Turning now to the rejection based upon the term "medicaments", the applicants reply that this term is employed in claims 8, 10, and 11, and in each claim the language used is clear. Note that the claims recite medicaments comprising at least one compound of the general formula (I) plus some other material. Accordingly, it is clear that these are claims to pharmaceutical compositions. It is requested that the rejection under §112 be withdrawn.

Finally, with respect to claim 6, the definition of "D" in structure (II) has now been corrected by amending "R^{38}" to read "R^{35}" in accordance with the text of the specification at pages 27-28. In addition, the section labels of the claim originally shown as [A], [B], [C], and

[D] respectively have been revised to read (A), (B), (C), and (D) respectively to avoid confusion as to whether the brackets indicate material which is to be deleted. In view of the correction of R^{38} to read R^{35}, withdrawal of the rejection of claim 6 under §112 is requested.

The rejection under 35 USC §103

In the official action, the examiner has rejected claims 1, 13-15, 17, and 18 under §103(a) as unpatentable over Straub '507 and Straub '619, two PCT publications of Bayer AG.

According to the examiner, Straub '507 "describes a wide range of possible substituents in the substitution pattern on the 6-membered heterocycle in position 3 of the pyrazole ring..." and "no direct reference is made to cycloalkyl groups as possible substituents", ... "according to Straub, phenyl and even functional groups can be taken into consideration as well as alkyl groups without impairment of the biological activity..." Regarding the '619 Straub reference, the examiner states it teaches that "pyrazolo[3,4-b]pyridines or indazole derivatives, substituted *inter alia* with pyrimidinyl groups in position 3 of the pyrazole unit, are presented as agents for the treatment of cardiovascular diseases, (and) the substitution of the heterocyclic ring in position 3 of the condensed pyrazole ring is left fairly open..." The examiner concludes that "A person skilled in the art would therefore regard the incorporation of the cycloalkyl group instead of an alkyl or phenyl group in the compounds described in WO '507 as a conventional alternative measure for solving the technical problem of interest. This type of minor structural modification of a group of already known compounds with identical biological properties can, however, only be considered to be inventive if the use of the distinguishing structural feature produced unexpected effects or properties compared with the already known compounds."

The examiner's rejection under §103 does not meet the legal requirements for a proper prima facie obviousness rejection, because the cited references do not suggest making the presently-claimed compounds. Accordingly, it is requested that the rejection be withdrawn.

Straub '507 discloses and claims an extensive listing of possible substituents which may be located on the group R^1 when this is a 6-membered heterocycle attached to the 3-position of the core pyrazole ring, but the reference does not mention or claim alkyl groups as possibilities for such substituents. The possibility of alkyl substituents on the 6-membered heterocycle is only

raised by certain of the exemplary compounds, and in those compounds, the only alkyl group illustrated is methyl, not cycloalkyl as required by the present claims. In addition, when the 6-membered heterocycle is a pyrimidinyl group, methyl is shown as only one of 10 possible substituent groups. Thus, the Straub '507 reference, standing alone, does not suggest the presently-claimed compounds, in which at least one of the substituents R^1, X, and Y must be saturated or partially unsaturated C_3-C_8 cycloalkyl.

The Straub '619 reference discloses and claims an extensive listing of possible substituents which may be located on the group R^1 when this is a 6-membered heterocycle attached to the 3-position of the core pyrazole ring, and includes straight-chain or branched alkyl groups as possible substituents. However, the only substituent shown for the case when the 6-membered heterocycle is pyrimidinyl is methyl, not cycloalkyl as required by the present claims. The possibility of cycloalkyl substituents is not raised by this reference, or suggested by it.

The Straub '619 reference taken in combination with the '507 reference does not provide the legally required suggestion to make the presently-claimed compounds. Both references recite broad generic descriptions covering large numbers of possible compounds and provide exemplary compounds, but neither reference suggests that cycloalkyl groups should be employed as substituents on the heterocyclic group R^1 when this is a pyrimidinyl group.

The examiner has not cited any art which teaches that the presence of cycloalkyl groups as substituents on pyrimidinyl groups in the type of compounds here claimed is desirable. Instead, the examiner appears to take the position that when cited references disclose a large number of substituent groups which possibly may be employed on a particular part of a molecule, then other substituent groups which he considers to be structurally similar to certain of the disclosed substituent groups are obvious as "a conventional alternative". This is not the law. The cases hold that a proper prima facie conclusion of obviousness requires that the art, taken together with the skill of one skilled in the art, must suggest that the claimed compounds should be made, with an expectation of success in achieving the desired results. The cases also hold that "obvious to try" is not a proper standard. In the present application, the references taken separately or in combination do not suggest that the presently-claimed compounds, which require the presence of a cycloalkyl substituent, should be made. That other possible substituents

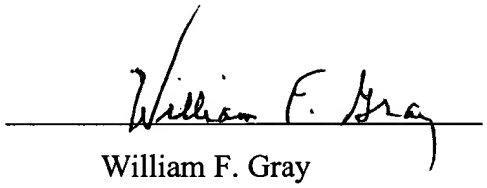
besides those disclosed in the cited references exist which might serve for the intended purpose does not make using those substituents obvious absent a suggestion that they should be employed. That suggestion is not present here.

The examiner's statement that "This type of minor structural modification of a group of already known compounds with identical biological properties can, however, only be considered to be inventive if the use of the distinguishing structural feature produced unexpected effects or properties compared with the already known compounds" is also incorrect. The law is clear that objective evidence of nonobviousness in not required unless the examiner has made out a proper prima facie case of obviousness, and even then, there are potentially several sorts of evidence which may serve to overcome the rejection. Unexpectedly good results is but one of these. In any event, the applicants maintain that as the examiner has not made out a legally sufficient prima facie obviousness rejection, there is no need to submit objective evidence of nonobviousness.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,



Reg. No. 31018
Phone: (203) 812-2712
Date: 10 Jan 02

William F. Gray
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Version with markings to show changes made:

In the claims:

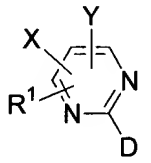
Claim 6 has been amended as shown below:

6. (Amended) Process for preparing the compounds of the general formula (I) according to Claim 1,

characterized in that

depending on the various meanings of the heterocycles listed above are under R^2 and R^3,

[[A]] (A) compounds of the general formula (II)



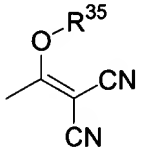
(II),

in which

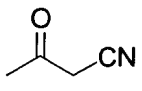
R^1, X and Y are each as defined above in Claim 1,

and

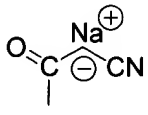
D represents radicals of the formulae



,



or



,

in which

[R^{38}] $\underline{R^{35}}$ represents C_1-C_4-alkyl

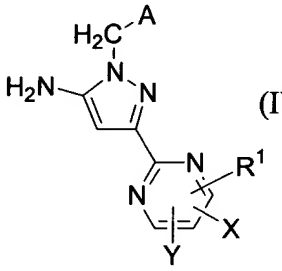
are converted, by reaction with compounds of the general formula (III)

$$A\text{-}CH_2\text{-}NH\text{-}NH_2 \qquad (III),$$

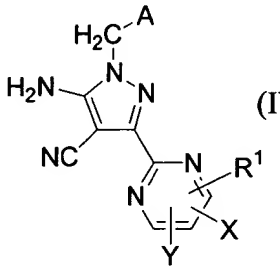
in which

A is as defined above in Claim 1,

in inert solvents into the compounds of the general formula (IV) or (IVa)



(IV) and



(IVa) ,

in which

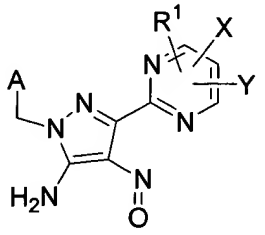
A, X, Y and R^1 are each as defined above in Claim 1,

and, in the case of the compounds of the general formula (IVa), are subsequently cyclized with carboxylic acids, nitriles, formamides or guanidium salts,

and in the case of the compounds of the general formula (IV), are cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, enol ethers or enamines in the presence of acids

or

[[B]] (B) in the case that R^2 and R^3 together form a pyrazine ring, compounds of the general formula (IV) are initially converted by nitrosation into the compounds of the general formula (V)

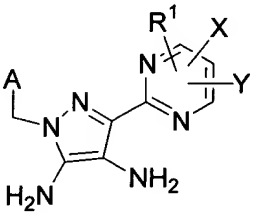


(V),

in which

A, X, Y and R^1 are each as defined above in Claim 1,

in a second step, the compounds of the general formula (VI)



(VI),

in which

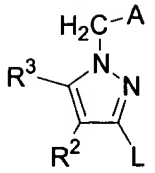
A, X, Y and R^1 are each as defined above in claim 1,

are prepared by a reduction,

and these are subsequently cyclized with 1,2-dicarbonyl compounds,

or

[[C]] (C) compounds of the general formula (VII)



(VII) ,

in which

[A^1] A , R^2 and R^3 are each as defined above in Claim 1,

and

L represents a radical of the formula $-SnR^{36}R^{37}R^{38}$, ZnR^{39}, iodine, bromine or triflate,

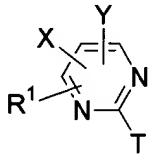
in which

R^{36}, R^{37} and R^{38} are identical or different and each represents straight-chain or branched alkyl having up to 4 carbon atoms

and

R^{39} represents halogen

are reacted with compounds of the general formula (VIII)



(VIII) ,

in which

X, Y and R^1 are each as defined above in Claim 1,

and

in the case that L = $SnR^{36}R^{37}R^{38}$ or ZnR^{39},

T represents triflate or represents halogen,

and,

in the case that L = iodine, bromine or triflate,

T represents a radical of the formula $SnR^{36'}R^{37'}R^{38'}$, $ZnR^{39'}$ or [$BR^{40'}R^{41'}$] $\underline{BR^{40}R^{41}}$,

in which

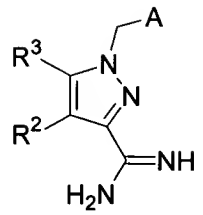
$R^{36'}$, $R^{37'}$, $R^{38'}$ and $R^{39'}$ have the meanings of R^{36}, R^{37}, R^{38} and R^{39} given above in Claim 1 and are identical to or different from them,

R^{40} and R^{41} are identical or different and each represent hydroxyl, aryloxy having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy having in each case up to 5 carbon atoms, or together form a 5- or 6-membered carbocyclic ring

in a palladium-catalyzed reaction in inert solvents,

or

[[D]] (D) amidines of the general formula (IX)

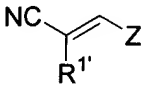


(IX) ,

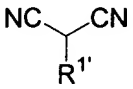
in which

A, R^2 and R^3 are each as defined above in Claim 1,

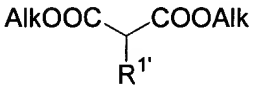
are reacted with compounds of the general formula (X), (Xa), (Xb) or (Xc)



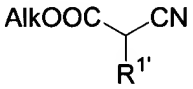
(X)



(Xa)



(Xb)



(Xc)

in which

$R^{1'}$ represents the optionally substituted cycloalkyl radical listed above under R^1,

Alk represents straight-chain or branched alkyl having up to 8 carbon atoms,

and

Z represents an NH_2 group, a monoalkylamino group having up to 7 carbon atoms, a dialkylamino group having up to 7 carbons, a piperidinyl or morpholinyl radical which is attached via the nitrogen, hydroxyl, alkoxy having up to 7 carbon atoms, acyloxy having up to 7 carbon atoms or aroyloxy having 6 to 10 carbon atoms,

and the substituents listed under X, Y, R^1, R^2, and R^3 and/or A are modified or introduced by acylation and derivatization of free amino groups, chlorination, catalytic hydrogenation, reduction, oxidation, removal of protective groups and/or nucleophilic substitution.